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COMMENTARY

Evidence already exists for motor system reorganization in CRPS

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ABSTRACT

Complex regional pain syndrome (CRPS) is a disabling condition that is usually preceded by trauma or surgical procedure. Involvement of the motor system is a well-known phenomenon in CRPS, though the pathophysiologic mechanisms of motor system affliction in CRPS are poorly understood. Graded motor imagery (GMI) has been proposed to be one of the therapeutic interventions to help improve pain and other disabling symptoms associated with CRPS, though the benefits noted are modest and inconsistent. The neurophysiological mechanisms implicated in motor imagery are intended to target the aberrant prefrontal and sensorimotor integration areas, which may potentially help restore the aberrant cortical plasticity in CRPS. Detailed well-controlled experiments using insights from the existing body of literature on motor system reorganization in CRPS are required to better understand this complicated disorder. Attempts to gain pathophysiologic insights about complicated disorders like CRPS based on case reports with poorly performed and uncontrolled interventions are misguided.

RÉSUMÉ

Le syndrome douleureux régional complexe est une affection invalidante habituellement précédée d'un traumatisme ou d'une intervention chirurgicale. L'implication du système moteur dans le SDRC est un phénomène bien connu, malgré le fait que les mécanismes pathophysiologiques qui l'affectent soient mal compris. L'imagerie motrice progressive (IMP) a été proposée en tant que l'une des interventions théraeutiques pouvant aider à améliorer la douleur et d'autres symptômes invalidants associés au SDRC, bien que les effets bénéfiques observés soient modestes et contradictoires. Les mécanismes neurophysiologiques impliqués dans l'imagerie motrice sont destinés à cibler l'aire préfrontale et l'aire d'intégration sensorimotrice anormales qui peuvent potentiellement aider à rétablir la plasticité corticale dans le SDRC. Des expériences approfondies bien contrôlées fondées sur les connaissances que l'on retrouve dans la littérature existante en ce qui concerne la réorganisation du système moteur dans le SDRC sont nécessaires afin de mieux comprendre ce trouble compliqué. Les tentatives pour améliorer les connaissances pathophsyiologiques concernant des troubles compliqués comme le SDRC qui sont fondées sur des études de cas et des interventions effectuées de manière médiocre et non contrôlées sont malavisées.

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Complex regional pain syndrome (CRPS) was first described by Weir Mitchell as a vasomotor neurosis and he has been credited for first using the term *causalgia* in his writing to describe the symptoms associated with this rather elusive disorder.[1–5] CRPS still remains a poorly understood and disabling condition.[6–8] It is usually preceded by minor to severe trauma or surgical procedure.[9–11] Involvement of the motor system is a well-known phenomenon in CRPS, though the pathophysiologic mechanisms involved are poorly understood.[12–17] Movement disorders in CRPS have been variously described as loss of voluntary control or failure to initiate movement, weakness, bradykinesia, dystonia, myoclonus, spasm, and tremor.[18–20] The current literature, which includes studies based on noninvasive brain stimulation techniques like transcranial magnetic stimulation (TMS), support increased cortical excitability in CRPS, and normalizing these cortical aberrancies can potentially help improve the motor performance in CRPS.[21–23]

In the present issue of the *Canadian Journal of Pain*, Harvey et al. describe the case of a 58-year-old woman who developed CRPS after sustaining a radial fracture.[24] They treated her with graded motor imagery and noted some improvements in her pain without any significant objective improvement in the motor disability. They additionally performed TMS during the follow-up visits and noted a serial increase in delta scores based on motor evoked potential (MEP) amplitudes

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and interpreted that as being evidence for motor system reorganization. The current case, which occurred after a radial fracture was classified as CRPS type I; however, the authors do not report any findings of electromyography (EMG)/nerve conduction studies, which would be essential for this diagnosis, especially in the setting of a fracture. Absence of baseline and follow-up nerve conduction studies to rule out the possibility of any axonotmesis or neurapraxia makes the interpretation of the findings of the current case report difficult. The authors correctly noted many limitations in their performance and interpretation of the TMS experiments. To note a few, they used delta scores derived using resting motor threshold (RMT) as a surrogate for corticospinal strength, which is incorrect. They did not perform an input-output (IO) curve, which involves giving TMS pulses of varying strengths in a random order to measure the MEPs at the different stimulation intensities. Additionally, using the same swim cap to locate the hotspot for follow-up visits is an erroneous technique. Though using swim caps may be reasonable technique for a single session, it is certainly not appropriate for multiple follow-up visits, and imaging-based guidance should have been used to ensure stimulation of the same cortical site.

The authors suggested improvements noted in delta scores that are based on RMT obtained at follow-up visits as suggestive of strengthening of corticospinal projections. RMT is increased by drugs blocking the voltage-gated sodium channels and decreased by drugs that enhance non-N-methly-D-aspartate (NMDA)-mediated glutamatergic transmission.[25–27] There is no clear evidence that any of the interventions performed by the authors influence either of these mechanisms. Mechanisms of graded motor imagery, though poorly understood, implicate influencing the prefrontal and sensorimotor integration cortices.[28–30] Studying the influence of a complicated therapeutic intervention using measures based on RMT does not have any clear rationale. The authors claim improvements in the MEP recorded as evidence of strengthening of corticospinal projections; however, the clinical improvements in strength are clearly lacking.

The findings of the current case report can be best interpreted as improved recording of the surface EMG as the vasomotor and sudomotor changes associated with CRPS improved. Though the authors noted non-significant changes in the edema, the peripheral changes were not clearly monitored objectively at follow-up, to be certain. Though the changes related to edema can affect the MEPs at both 110% and 130%, the variability in the MEPs is higher at intensities between 120% and 140% RMT and, as a result, the delta scores may be further falsely inflated.[31] Another possible explanation could be the resolution of the nerve damage, which may have occurred due to the fracture and would follow a similar timeline for improvement.[32] Improvement in the strength of corticospinal projections is an unlikely explanation for the findings noted in the current report.

Evidence does exist for motor system reorganization in CRPS and I reference some of the current literature on the subject in this write-up. The efforts by the authors to find objective measures to corroborate improvements in motor function are commendable. However, interpretation of their findings as evidence for motor system reorganization is misguided in my opinion.

Disclosure of Interest

Shabbir Hussain Merchant has no relevant conflict of interest to declare related to this publication.

References

1. Mitchell SW, Morehouse GR, Keen WW. The classic. Gunshot wounds and other injuries of nerves by S. Weir Mitchell, MD, George R. Morehouse, MD, and William W. Keen, MD. Clin Orthop Relat Res. 1982;2–7.
2. Mitchell SW. Injuries of nerves and their consequences. Philadelphia (PA): J.B. Lippincott & Co.; 1872.
3. Richards RL. The term "causalgia." Med Hist. 1967;11:97–99. doi:10.1017/S0025727300011789.
4. Causalgia RRL. A centennial review. Arch Neurol. 1967;16:339–350. doi:10.1001/archneur.1967.00470220003001.
5. Mitchell SW. On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confounded. Am J Med Sci. 1878;151:17–36. doi:10.1097/00000441-187815100-00001.
6. Schwartzman RJ, Alexander GM, Grothusen J. Pathophysiology of complex regional pain syndrome. Expert Rev Neurother. 2006;6:669–681. doi:10.1586/14737175.6.5.669.
7. Gibbs GF, Drummond PD, Finch PM, Phillips JK. Unravelling the pathophysiology of complex regional pain syndrome: focus on sympathetically maintained pain. Clin Exp Pharmacol Physiol. 2008;35:717–724. doi:10.1111/j.1440-1681.2007.04862.x.
8. Mrabet D, Khemiri C, Ben Mrad I, Mrabet H, Essaddem H, Amel M, Sahli H, Sellami S. [Pathophysiology of complex regional pain syndrome (CRPS) type 1]. Tunis Med. 2012;90:278–281.
9. Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. Pain. 1999;80:539–544. doi:10.1016/S0304-3959(98)00246-2.

10. Choi YS, Lee MG, Lee HM, Lee CJ, Jo JY, Jeon SY, Lee SC, Kim YC. Epidemiology of complex regional pain syndrome: a retrospective chart review of 150 Korean patients. J Korean Med Sci. 2008;23:772–775. doi:10.3346/jkms.2008.23.5.772.
11. Pappagallo M, Rosenberg AD. Epidemiology, pathophysiology, and management of complex regional pain syndrome. Pain Pract. 2001;1:11–20. doi:10.1046/j.1533-2500.2001.01003.x.
12. Munts AG, Mugge W, Meurs TS, Schouten AC, Marinus J, Moseley GL, Van Der Helm FC, Van Hilten JJ. Fixed dystonia in complex regional pain syndrome: a descriptive and computational modeling approach. BMC Neurol. 2011;11:53. doi:10.1186/1471-2377-11-53.
13. Bank PJ, Peper CE, Marinus J, Van Hilten JJ, Beek PJ. Intended and unintended (sensory-)motor coupling between the affected and unaffected upper limb in complex regional pain syndrome. Eur J Pain. 2015;19:1021–1034. doi:10.1002/ejp.668.
14. Bank PJ, Peper CL, Marinus J, Beek PJ, van Hilten JJ. Deficient muscle activation in patients with complex regional pain syndrome and abnormal hand postures: an electromyographic evaluation. Clin Neurophysiol. 2013;124:2025–2035. doi:10.1016/j.clinph.2013.03.029.
15. Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol. 2011;10:637–648. doi:10.1016/S1474-4422(11)70106-5.
16. van Rijn MA, Marinus J, Putter H, Van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. Pain. 2007;130:287–293. doi:10.1016/j.pain.2007.03.027.
17. Schilder JC, Schouten AC, Perez RS, Huygen FJPM, Dahan A, Noldus LPJJ, Van Hilten JJ, Marinus J. Motor control in complex regional pain syndrome: a kinematic analysis. Pain. 2012;153:805–812. doi:10.1016/j.pain.2011.12.018.
18. van Hilten JJ. Movement disorders in complex regional pain syndrome. Pain Med. 2010;11:1274–1277. doi:10.1111/j.1526-4637.2010.00916.x.
19. Agrawal SK, Rittey CD, Harrower NA, Goddard JM, Mordekar SR. Movement disorders associated with complex regional pain syndrome in children. Dev Med Child Neurol. 2009;51:557–562. doi:10.1111/j.1469-8749.2008.03181.x.
20. Abu-Arafeh H, Abu-Arafeh I. Complex regional pain syndrome in children: a systematic review of clinical features and movement disorders. Pain Manag. 2017;7:133–140. doi:10.2217/pmt-2016-0036.
21. Nardone R, Brigo F, Holler Y, Sebastianelli L, Versace V, Saltuari L, Lochner P, Trinka E. Transcranial magnetic stimulation studies in complex regional pain syndrome type I: a review. Acta Neurol Scand. 2017;158–164. doi:10.1111/ane.12852.
22. Krause P, Foerderreuther S, Straube A. Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. Neurology. 2004;62:1654–1655. doi:10.1212/WNL.62.9.1654.
23. Eisenberg E, Chistyakov AV, Yudashkin M, Kaplan B, Hafner H, Feinsod M. Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. Pain. 2005;113:99–105. doi:10.1016/j.pain.2004.09.030.
24. Harvey MP, Maher-Bussières S, Elysa Emery, Martel M, Houde F, Tousignant-Laflamme Y, Léonard G. Evidence for motor system re-organization in CRPS type-I: a case report. Can J Pain. 2018;2(1):21–26. doi:10.1080/24740527.2017.1422116.
25. Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol. 1996;40:367–378. doi:10.1002/ana.410400306.
26. Ziemann U, Tergau F, Bruns D, Baudewig J, Paulus W. Changes in human motor cortex excitability induced by dopaminergic and anti-dopaminergic drugs. Electroencephalogr Clin Neurophysiol. 1997;105:430–437. doi:10.1016/S0924-980X(97)00050-7.
27. Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, Rothwell JC. Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. Clin Neurophysiol. 2000;111:794–799. doi:10.1016/S1388-2457(99)00314-4.
28. Decety J. The neurophysiological basis of motor imagery. Behav Brain Res. 1996;77:45–52. doi:10.1016/0166-4328(95)00225-1.
29. Gieteling EW, Van Rijn MA, De Jong BM, Hoogduin JM, Renken R, Van Hilten JJ, Leenders KL. Cerebral activation during motor imagery in complex regional pain syndrome type 1 with dystonia. Pain. 2008;134:302–309. doi:10.1016/j.pain.2007.04.029.
30. Jeannerod M, Decety J. Mental motor imagery: a window into the representational stages of action. Curr Opin Neurobiol. 1995;5:727–732. doi:10.1016/0959-4388(95)80099-9.
31. Davey NJ, Smith HC, Savic G, Maskill DW, Ellaway PH, Frankel HL. Comparison of input–output patterns in the corticospinal system of normal subjects and incomplete spinal cord injured patients. Exp Brain Res. 1999;127:382–390. doi:10.1007/s002210050806.
32. Burnett MG, Zager EL. Pathophysiology of peripheral nerve injury: a brief review. Neurosurg Focus. 2004;16:E1. doi:10.3171/foc.2004.16.5.2.